New, Ultrasensitive, SQUID-Based Magnetic Sensor Developed

Using an exquisitely sensitive magnetic field detector, an LBNL team of physicists, chemists and biochemists has developed a new sensor that is selective, easy to use, rapid, and extraordinarily sensitive. The first prototype required fewer than 30,000 targets to generate a reproducible signal. A several order of magnitude further increase in sensitivity is expected.

The new technique relies on a microscope with a high-T_c superconducting quantum interference device (SQUID) that detects the binding of magnetic nanoparticles to the target. In contrast with other techniques, such as fluorescence, unbound particles do not give a signal, thus no "wash" step to remove them from the detector, is required.

The prototype experiment was performed using a microscope fabricated with a SQUID using the high-Tc superconducting material yttrium-barium-copper oxide. Despite the fact that the SQUID must be maintained at liquid nitrogen temperatures, about 77 Kelvin, or -196 C, design of the microscope is such that it can be brought within micrometers of the room temperature samples to be detected without damaging them.

Superparamagnetic, 35nm iron oxide particles were used as probes. When exposed to an external magnetic field they become magnetized and align along the field lines. When the field is turned off, those particles whose motion is not restrained undergo so-called Brownian rotation causing their magnetic moments to cancel each other within microseconds, before the microscope can detect them. However, if the particles are immobilized, for example attached to a target that is in turn bound to a surface, the magnets cannot physically rotate. Instead, the spins of the individual atoms in the nanoparticle—the source of its magnetic dipole moment—reorient themselves in a process called Néel relaxation, which also leads to a loss of the magnetic signal. With the superparamagnetic particles used here, this phenomenon is slower, on the order of seconds, and can be monitored by the microscope.

The target selected for the initial study was an artificial cell (liposome) with a specific protein (FLAG) extending out from its membrane. Antibodies that selectively bind FLAG were attached to the magnetic nanoparticles. When the liposomes and magnetic particles were mixed in the well of the microscope above a thin sheet of mylar, the liposomes bound to the mylar and the magnetic particles bound to the liposomes and became immobilized. A one second magnetic pulse was applied (see figure) and the magnetic signal from the particles was monitored, also for one second. A clear signal of Néel relaxation was observed (see figure). In the absence of liposomes, or in the presence of liposomes lacking FLAG on their surface, no signal was seen—the unbound magnetic particles randomized by Brownian motion before their signal could be detected. The signal was shown to scale with the number of particles or number of liposomes.

The technique is rapid: it requires only one second to magnetize the particles and one second to detect the signal from those that become bound. Calculations and also visualization of the particles in a transmission electron microscope confirmed that no more than 30,000 immobilized magnetic particles were needed for the signal to be detected. The number of liposomes required was far fewer, since each carried many copies of the target protein and thus bound many magnetic particles. Standardization curves relating the number of particles immobilized to number of targets present will be prepared.

Moreover, refinements to the instrument and procedure now in progress should improve the sensitivity of the new technique and allow detection of as few as 50 to 500 magnetic particles, and consequently, even fewer targets. In addition, an array of samples could potentially be scanned over the SQUID, resulting in enhanced speed and versatility. By providing information in "real time", the technique could serve for detection of biological or chemical warfare agents, monitoring of food processing lines or diagnosis of infectious disease.

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